

DETAILED ACTION
RESPONSE TO ELECTION/RESTRICTION

Applicant's election of a new compound group XXV (wherein X_1 = alkynylene, X_2 = X_3 = Y = a bond, and L = substituted carbocyclic ring) and election of specie (example 39 of the specification) in the reply filed on 3/23/2009 is acknowledged. The elected specie reads on claims 1-6, 19, 20, 35, and 36. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 7-18, 21-34, and 37-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application contains claims drawn to an invention nonelected without traverse in the reply filed on 3/23/2009. A complete reply to this action must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's elected specie was found free of the prior art, thus the full scope of the claims are examined.

An action on the merits of claims 1-6, 19, 20, 35, and 36 is contained herein.

Priority

This application receives the priority date of 4/9/2003, drawn to provisional application 60/461,546.

Specification

The disclosure is objected to because of the following informalities: The first paragraph in the Specification should indicate up-to-date claims of benefit to priority U.S. Applications. Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11. Appropriate correction is required.

Claim Objections

Applicant is advised that should claim 19 be found allowable, claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, from first glance, claims 19 and 20 both encompass the same chemical species.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 1-6 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and only their pharmaceutical salts wherein A = aryl or furanyl, R^{1-3} = hydrogen, and L = the carbocyclic ring seen in claim 1 that may be substituted with R' (wherein R' is hydrogen, halo, hydroxy, amino, or alkyl), does not reasonably provide enablement for the other thousands of compounds that applicant is claiming. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

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Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. Analysis is described below:

(A) Breadth of claims: The formula I is drawn to a myriad of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, acidity, basicity, and properties that are known in the art to greatly influence pharmacokinetic and pharmacodynamic parameters, not to mention the ability to productively bind to claimed biological target molecules. The claims cover compounds easily in the millions given the number of possible rings, ring systems covered by the claims' scope along with varying choices for remaining variables; thus the claims are very broad.

(B) The nature of the invention: Triazolopyrazines that act as antagonists of A_{2a} subtype adenosine receptors for treating a plethora of neurodegenerative diseases.

(C) State of the Prior Art: Chemistry is unpredictable. See *In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed

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smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task.

In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such workChemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)" Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(D) Skill of those in the art: The level of skill in the art is high.

(E) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(F) Direction or Guidance: Little guidance or direction is provided by applicant in reference to making compounds that did not possess the substituents cited previously. The presence of various bulky heterocyclic or carbocyclic rings attached to the compound's core may be chemically incompatible with the method of use embraced in the instant claims. Specification offers no teachings or suggestion as to how to make and use these compounds. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of

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inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.";

(G) Working Examples: The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed. Applicant has provided no working examples of any compounds where the compound of formula I did not contain the variables previously mentioned above in the present application.

The specification gives some *in vitro* test results on A_{2a} subtype adenosine receptor inhibitory effects of a limited number of preferable compounds, however it is too homogeneous to provide a clear evaluation of which moieties attached to the compound's core out of the many claimed might affect potency to a large or small degree. The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. Extremely broad generalizations as found in the instant claims are in contradiction with the basis of quantitative structure-activity-relationship (QSAR).

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability

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or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

(H) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome. Applicant fails to provide guidance and supporting information for how to make and/or use the thousands of other compounds which are encompassed by the claims, therefore undue experimentation would be expected.

Due to the level of unpredictability in the art, the very limited guidance provided, and the lack of working examples, the applicant has shown lack of enablement. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Conclusion

No claims are allowed.

Claims 19, 20, and 36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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Reasons for Allowance

Claims 19, 20, 36 are novel in respect to the species embraced within, wherein said species encompass a fused bicyclic core where the *6-membered heterocyclic ring is a pyrazine*.

The limitations listed supra represent the limitations that are not taught or fairly suggested by the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is (571)270-5755. The examiner can normally be reached on Monday-Thursday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/B. M./

Examiner, Art Unit 1624

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624

